REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Status of the Claims

Upon entry of the present Amendment, claims 1, 4, 15, 17-20, 23-26 and 35-41 will be pending.

Independent claims 1 and 35 have been amended to recite one embodiment of the present invention. Specifically, independent claims 1 and 35 require a pharmaceutical dosage form comprising metformin hydrochloride and pioglitazone hydrochloride. The dosage form comprises (a) a controlled release core; (b) optionally a seal coating surrounding the core; and (c) an immediate release pioglitazone layer. The controlled release core comprises (i) a core comprising a pharmaceutically acceptable excipient and metformin hydrochloride and (ii) a sustained release coating. The immediate release pioglitazone layer comprises pioglitazone and a binder and is free of a surfactant. The immediate release pioglitazone layer also releases not less than 90% of the pioglitazone hydrochloride within 30 minutes of *in vitro* testing; after storage for three months at 40°C and 75% relative humidity, the total of pioglitazone related compounds or impurities present in the dosage form is not more than 0.6%, and each individual pioglitazone related compound or impurity is not more than 0.25%.

No new matter is added by the present amendments.

Support for the not less than 90 % of the pioglitazone hydrochloride being released within 30 minutes of *in vitro* testing can be found in claim 10 as originally filed; page 12, lines 10-15 of the specification; and Example 6 on pages 23-27 of the specification.

Support for the immediate release pioglitazone layer being free of a surfactant can be found on page 11, lines 15-20, which indicates the immediate release thiazolidinedione or pioglitazone layer may contain 0-20 wt% of a surfactant, and Examples 5 and 6 on pages 21-27 of the specification, which describe embodiments of the currently claimed invention that comprise an immediate release pioglitazone layer without a surfactant.

Double Patenting

On pages 2-3 of the Office Action, the Examiner provisionally rejected claims 1, 4, 15, 17-20, 23-26 and 35-41 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-50 and 55-63 of co-pending Application No. 11/093,742 (hereinafter "the '742 application").

Applicants acknowledge the Examiner's provisional double patenting rejection and respectfully request that the rejection be held in abeyance until a finding of allowable subject matter is found in the present application.

If the Examiner believes the present amendments and following remarks place the claims in condition for allowance, except for the provisional double patenting rejection, the undersigned respectfully requests a telephone interview to discuss the provisional double patenting rejection and ways to expedite allowance of the present application.

35 U.S.C. § 103 (a)

On page 4 of the Office Action, the Examiner rejected the pending claims under 35 U.S.C. § 103(a) as being unpatentable over Lewis, WO 01/35940 (hereinafter "Lewis") in view of Timmins, WO 99/47128 (hereinafter "Timmins").

Reconsideration is requested in view of the present amendments and remarks.

Applicants respectfully submit the pending claims are patentable over the combination of Lewis and Timmins because the combination of Lewis and Timmins does not disclose or suggested to a skilled artisan a controlled release metformin hydrochloride and immediate release pioglitazone hydrochloride dosage form that employs: 1) a sustained release coating to control the release of the metformin hydrochloride; 2) an immediate release pioglitazone hydrochloride layer that is free of a surfactant; 3) an immediate release pioglitazone hydrochloride layer that releases not less than 90% of the pioglitazone hydrochloride within 30 minutes of *in vitro* testing; and 4) a dosage form wherein after storage for three months at 40°C and 75% relative humidity, the total of pioglitazone-related compounds or impurities is not more than 0.6%, and each individual pioglitazone-related compound or impurity is not more than 0.25%. It is further submitted that the combination of Lewis and Timmins would not motivate a skilled artisan to prepare a dosage form with the aforementioned features with a reasonable expectation of success.

Lewis, the primary reference relied upon by the Examiner, provides a very general teaching for preparing dosage forms containing an immediate release dose of metformin hydrochloride and an immediate release dose of a thiazolidinedione such as pioglitazone hydrochloride. Lewis teaches that the thiazolidinedione, such as pioglitazone hydrochloride, may be dissolved in a solvent along with "Opadry" and applied to the surface of the metformin hydrochloride. *See* Lewis at p. 5, lines 1-7. "Opadry" is a tradename for a commercially available line of pharmaceutical coatings. *See* Exhibit A hereto, which is a printout of Colorcon's website advertising the OPADRY® line of products. The passage from Lewis fails to provide the skilled artisan with any guidance for selecting an appropriate OPADRY® material or for employing the OPADRY® material to apply a stable immediate release pioglitazone layer to a sustained release coated metformin core.

The addition of Timmins to Lewis fails to overcome the deficiencies of Lewis and lead a skilled artisan to the presently claimed dosage form with an expectation of success.

Timmins discloses a biphasic extended release dosage form that contains (1) an inner solid particulate phase containing an extended release material and a biguanide such as metformin hydrochloride and (2) an outer solid continuous phase in which the inner solid particulate phase is dispersed and embedded. *See* Timmins at pp. 14-15.

Although Timmins discloses a controlled release metformin core, Timmins does not disclose a controlled release metformin core surrounded by a sustained release coating as recited in the pending claims. Therefore, the combination of Timmins and Lewis as suggested by the Examiner will not lead a skilled artisan to the present invention which requires a controlled release core that comprises a metformin hydrochloride core and a sustained release coating surrounding the metformin hydrochloride core.

Like Lewis, Timmins provides a limited description for applying a thiazolidinedione coating to a metformin core. For example, Timmins teaches that a thiazolidinedione can be applied to the biphasic metformin core. *See* Timmins at pp. 21-22. Timmins provides little guidance to a skilled artisan for preparing the thiazolidinedione layer and, more importantly, no guidance for preparing a pioglitazone hydrochloride layer that is free of a surfactant, releases 90% of the pioglitazone hydrochloride within 30 minutes of *in vitro* testing and, after storage for three months at 40°C and 75% relative humidity,

exhibits a total of pioglitazone-related compounds or impurities of not more than 0.6% and each individual pioglitazone related compound or impurity of not more than 0.25%.

The teachings of Lewis and Timmins fail to disclose or suggest to a skilled artisan a dosage form that comprises an immediate release pioglitazone hydrochloride layer surrounding a sustained release coated metformin core wherein the immediate release pioglitazone layer is free of surfactant and releases 90% of the pioglitazone within 30 minutes of *in vitro* testing. As mentioned above, Lewis only teaches that the thiazolidinedione can be applied to the metformin with the aid of OPADRY®. This general disclosure of OPADRY® in Lewis does not provide any guidance to a skilled artisan regarding which grade or type of OPADRY® to use with pioglitazone hydrochloride. Some of the OPADRY® coatings may contain surfactants that Applicants have discovered can cause detrimental effects to pioglitazone hydrochloride upon storage. Support for the adverse effects of a surfactant on pioglitazone hydrochloride can be found in the following excerpt from a product development report submitted to the FDA seeking approval to market an embodiment of the present invention known as ACTOSPLUS MET® XR[1]:

A forced degradation study was performed to evaluate any possible interaction of pioglitazone HCl with the excipients contained in the drug layer formulation and with the coating formulation of the Metformin XT core tablet. More specifically, pioglitazone HCl was dry mixed with the various excipients at a weight ratio of 1:1. Triacetin was included in the study because it is used as a plasticizer in the sustained release (CA) coating of Metformin XT tablets. Polyethylene glycol 400 was also included in this study because it is used as a plasticizer in Opadry® Clear and Opadry® White. The mixtures were stored in open glass vials at 60°C/75% RH for 2 weeks. Table 1.b shows the experimental matrix with the impurity results.

Table 1.b Forced Degradation Study of Pioglitazone HCl and Formulation Excipients

	Amount in grams						
Vials	Control	1	2	3	4	5	Actos® 15 mg (Lot P1505296AC1
Pioglitazone HCl	1.00	1.00	1.00	1.00	1.00	1.00	
Opadry® Clear		1.00					
Polysorbate 80			1.00				
Sodium Chloride				1.00			
Triacetin					1.00		
Polyethylene glycol 400						1.00	
Total Impurity, %	0.11	0.15	0.51	0.02	0.02	0.05	0.16

[1] Applicants are not providing a complete copy of the product development report because it contains confidential information that Applicants do not wish to be made public at the present time. Applicants aver

The above table shows that polysorbate 80, a known surfactant, will cause the pioglitazone to degrade after only two weeks.

Even if a skilled artisan were fortunate enough to select an OPADRY® that was free of surfactant, combining the teachings of Lewis with Timmins would not necessarily result in the presently claimed invention. For example, on page 7, Lewis exemplifies a few metformin hydrochloride and thiazolidinedione compositions wherein the ratio of the OPADRY® to thiazolidinedione was 2:1. Applicants respectfully submit the large amount of OPADRY® to thiazolidinedione taught by Lewis will not necessarily result in an immediate release pioglitazone hydrochloride coating when surrounding a sustained release coated metformin core that releases not less than 90% of the pioglitazone hydrochloride within 30 minutes of *in vitro* testing.

The following excerpts from the previously discussed product development report show that immediate release pioglitazone layers applied to sustained release coatings of controlled release metformin cores as described in Examples 5 and 6 of the present specification are not predictable.

---

that the report has never been made available to the general public.

Table 1.c **Summary of Preliminary Formulations, Processing Conditions and Analytical Results of AD-4833XT Tablets, 30 mg/1000 mg**

Lot numbers	673F020	673F021	673F022	673F023	673F024	673F025	673F026	673F027	673F028	673F029
Metformin XT Tablets, 1000 mg (%)	93.74	93.74	94.1	93.74	93.74	93.95	93.46	93.46	93.46	93.41
Seal coating (%)										
Opadry® Clear	1.237	1.237	1.242	1.33	1.237	1.24	1.534	1.634	1.634	1.633
Solvent	Water	Water	Alcohol USP	Water	Water	Alcohol USP	Alcohol USP	Alcohol USP	Alcohol USP	Alcohol USP
Drug Layering (%)										
Pioglitazone HCl, equiv. to 30 mg pioglitazone	2.557	2.557	2.567	2.557	2.557	2.562	2.573	2.573	2.573	2.571
Polivinpirone K9	0.333	0.332	0	0.282	0.282	0	0	0	0	0
Sodium Chloride	0.498	0.498	0.332	0.498	0.498	0.388	0.389	0.389	0.389	0.389
Opadry® Clear	0.332	0.332	0.155	0.282	0.282	0.238	0.238	0.333	0.333	0.288
Solvent	Water	Water	Alcohol USP	Water	Water	Alcohol USP, Water	Alcohol USP Water	Alcohol USP Water	Alcohol USP Water	Alcohol USP Water
						9:1	7.5:2.5	7: 3	7:3	7.5:2.5
Color Coating and Polishing (%)										
Opadry II® White	1.477	1.477	1.474	1.477	1.477	1.592	1.674	1.674	1.674	1.672
Solvent	Water	Water	Alcohol USP	Water	Water	Alcohol USP	Alcohol USP	Alcohol USP	Alcohol USP	Alcohol USP
Candelilla Wax Powder	0.031	0.031	0.031	0.031	0.031	0.031	0.031	0.031	0.031	0.031
Operating Parameter										
% Overage	5	10	5	5	10	10	10	10	15	15
Batch size, Kg	13	13	13	13	13.8	14	14	14	14	14
# of Spray Guns	2	2	2	2	2	3	3	3	3	3
Spray rate, ml/gun/min	20	25	35	35	35	35	35-30	20-35	20-35	20-35
Nozzle Distance, inch	7	7	6	7	5	4	4	4	4	4
Inlet Air Temp, °C	42-43	47-49	34-39	40-42	53	33-39	37-38	39	37-47	36
Exhaust Air Temp, °C	30	33	30	30	35	24-27	28	30	34-38	28
Air Flow, CFM	300	250	300	300	250	250	200	250	300	300
Pan speed, rpm	9	9	9	7	8	6-7	6-7	5.5-6.5	6-6.5	5.5-6
Test Result:										
Appearance	Chipping	Chipping	Good	Fail	Edge defects	Edge defects	Good	Edge defects	Fail	Good
Potency Assay, %LC	n/a	n/a	n/a	n/a	n/a	93.5	92	97.3	98.9%	102.2
Content Uniformity										
Mean, %LC	90.3	98.2	92.4			94.5	84.6	83.6	95.2	98.6	104.6
Minimum, %LC	84.1	87.9	45.8			84.3	80.5	85.7	90.7	94.1	96.6
Maximum, %LC	101.5	111.7	96.6			98.2	93.1	102.4	101.8	104.7	116
RSD, %	6.3	7.2	7.6	n/a		4.6	4.1	5.2	3.9	4.0	4.4
%Dissolved @30 min	88	86	99	n/a		83	95	99	95	97	95
Total Pioglitazone R.C, %	n/a	n/a	n/a	n/a		n/a	0.12	n/a	0.2	n/a	0.17

Table 1.d Summary of AD-4833XT Non-surfactant Based Tablet Formulations, 30 mg/1000 mg, with Analytical Results

Drug Layering Formulation, mg/tab	572P029	SR3933-99	SR4109-76	SR4109-80	SR4109-85	SR4109-91	WSK0354-13
Pioglitazone	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Opadry Clear	3.7	-	-	-	-	-	-
Hallcoat IR	-	46.0	-	-	-	-	-
HPC-SSL	-	-	12.0	12.0	-	9.0	9.0
PEG8000	-	-	0.6	0.6	0.3	0.45	0.45
Klucel LF	-	-	-	-	6.0	-	-
Sodium Chloride	5.0	-	-	-	-	-	-
Lactose Monohydrate	-	-	100.0	100.0	105.0	39.0	39.0
Titanium dioxide	-	-	-	-	0.6	0.9	0.9
Unit coated	Yes	Yes	No	Yes	Yes	Yes	Yes
Color coated	Yes (Opadry II)	Yes (Opadry II)	Yes	Yes	No	No	Yes
% wt. Gain	8.8	8.8	11.3	11.9	11.1	6.5	6.97
Solvent	EtOH: Water 78:22	EtOH: Water 60:40	Water	Water	Water	Water	Water
% Overage	15	15	15	15	15	15	15
Equipment used	24" pan	24" pan	24" pan	24" pan	24" pan	24" pan	Vector
Qualitative assessment of appearance	Good	Good	Bumpy	Some bumps	Good	Good	Good
Dissolution, %							
5 min	n/a	34	55	33	59	33	22
10 min	42	55	89	69	78	69	49
15 min	n/a	42	93	78	87	89	81
20 min	76	47	94	80	92	94	95
30 min	95	57	95	81	95	96	97
	100 rpm Basket	50 rpm Paddles	50 rpm Paddles	50 rpm Paddles	50 rpm Paddles	50 rpm Paddles	50 rpm Paddles
Content Uniformity. Mean, %LC %RSD	104.6 4.4	n/a	n/a	n/a	106.3 5.4	107.0 5.3	107.0 5.8
Total RC initial	0.17	n/a	0.19	n/a	0.20	0.19	0.19
% Total Impurity (2 days at 60°C/75%RH)	n/a	n/a	0.18	n/a	0.18	0.19	0.19
Friability, %	0.00	n/a	0.05	0.00	0.00	0.00	0.01

n/a – data not available, only limited amounts of data were collected for some of the development formulations.

Table 1.c Summary of AD-4833XT Surfactant Based Tablet Formulations, 30 mg/1000 mg, with Analytical Results

Drug Layering Formulation, mg/tab	SR3933-71	SR3933-75	SR3933-78	SR3933-93	SR4109-34	SR4109-36	SR4109-65	SR4109-78	WSR0254-91	573P041
Pioglitazone	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Opadry Clear	3.7	3.7	3.7	3.7	-	-	-	-	-	-
Sodium lauryl sulfate	15.0	-	-	-	-	-	-	-	-	-
Polysorbate 80	-	15.0	-	-	-	-	-	-	-	-
Docusate Sodium	-	-	-	15.0	-	-	-	-	-	-
Klucel LF	-	-	-	-	-	-	-	1.5	-	-
HPC-SSL	-	-	-	-	7.5	7.5	-	-	-	-
Povidone K30	-	-	-	-	-	-	3.0	-	3.0	3.0
Poloxamer 188	-	-	15.0	-	15.0	15.0	15.0	15.0	15.0	15.0
Lactose Monohydrate	-	-	-	-	60.0	60.0	90.0	90.0	90.0	90.0
Explotab	-	-	-	-	15.0	-	30.0	30.0	30.0	30.0
Crospovidone	-	-	-	-	-	15.0	-	-	-	-
Seal coated	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Color coated	Yes (Opadry II)	Yes (Opadry II)	Yes (Opadry II)	Yes (Opadry II)	Yes (Opadry II)	Yes (Opadry II)	Yes (Opadry II)	Yes Opadry White	Yes Opadry White	Yes (HPC-SSL+TiO2)
% wt. gain	7.7	7.7	7.7	9.0	12.2	12.2	13.5	13.5	13.5	13.5
Solvent	EtOH: Water 78:22	EtOH: Water 78:22	EtOH: Water 78:22	EtOH: Water 78:22	EtOH: Water 80:20	EtOH: Water 80:20	Water	Water	Water	Water
Equipment used	24" pan	24" pan	24" pan	24" pan	Vactor	Vactor	24" pan	24" Pan	24" pan	24" pan
Qualitative Assessment of Appearance	Good	Good	Good	Good	Good	Good	Good	OK	Good	Good
Dissolution %	**pH 2.0, paddles at 50 rpm**									
5 min	8	23	31	19	40	14	27	22	29	44
10 min	14	36	51	36	63	24	56	58	69	77
15 min	19	47	64	49	76	32	82	75	89	97
20 min	20	58	74	58	84	37	91	84	95	100
30 min	25	70	83	69	90	45	96	96	97	103
Assay	n/a	n/a	100.0	n/a	n/a	n/a	n/a	n/a	n/a	106.1
Content Uniformity Mean, %LC %RSD	n/a	87.2 4.5	n/a	n/a	n/a	n/a	n/a	n/a	94.2 5.0	107.8 2.8
Total % Impurity (initial)	0.18	n/a	n/a	n/a	n/a	n/a	0.15	n/a	0.17	n/a
Total % Impurity (3 days at 60°C/75%RH)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.17	0.18
Friability, %	n/a	n/a	n/a	n/a	n/a	n/a	0.00	n/a	0.00	0.00

n/a=Data not available, only limited amounts of data were collected for some of the development formulations

Table 1.c demonstrates that the choice of solvent and amount of binder for application of the immediate release pioglitazone layer to the sustained release coated metformin core can affect the adhesion of the pioglitazone coating. For example, lot 573P022 (which employed alcohol as the solvent and 0.155% of OPADRY® Clear as the binder) resulted in approximately 52.4% of the labeled pioglitazone being applied to the

sustained release metformin core while lot 573P029 (which employed an alcohol:water (7.8:2.2) mixture and 0.288% of OPADRY® Clear) resulted in approximately 104.6% of the labeled pioglitazone being applied to the sustained release metformin core.

Table 1.d shows that increasing the amount of binder may not improve the adhesion or release of the immediate release pioglitazone layer. For example, lot 573P029 shows that 3.7 mg of OPADRY® Clear as a binder for 30 mg of pioglitazone (33.06 mg of pioglitazone hydrochloride) provides good adhesion of the pioglitazone to the sustained release coating and a quick release of the pioglitazone while lot SR3933-99 (which employs 40 mg of Kollicoat IR as a binder for 30 mg of pioglitazone (33.06 mg of pioglitazone hydrochloride)) results in a slow release of pioglitazone or poor adhesion.

Table 1.e compares the effects of four surfactants in an immediate release pioglitazone hydrochloride layer. The four surfactants are sodium lauryl sulfate, polysorbate 80, docusate sodium and poloxamer 188. The results in table 1.e indicate that the anionic surfactants slowed the pioglitazone release rate. The data in Table 1.e also suggests that the poloxamer 188 formulation may exhibit acceptable release characteristics; however, it was later determined that the poloxamer 188 formulation was not stable on storage. *See* Exhibit B, Declaration of Kazuhiro Okochi Under 35 U.S.C. § 1.132, submitted in U.S. Patent Application No. 11/093,742 wherein Formulation C (which employs poloxamer 188 in the immediate release pioglitazone layer) exhibited 0.75% of total impurities after storage at 40°C and 75% relative humidity for 3 months.

Based upon the forgoing arguments and data, Applicants respectfully submit a skilled artisan would not be motivated to combine Lewis and Timmins and arrive at the presently claimed invention with an expectation of success. There is no disclosure provided in either Lewis or Timmins that would lead a skilled artisan to prepare a controlled release metformin core comprising a sustained release coating. In addition, there are no teachings in either Lewis or Timmins that would direct a skilled artisan to surround a sustained release coated metformin core with an immediate release pioglitazone hydrochloride layer that is free of a surfactant and releases not less than 90% of the pioglitazone within 30 minutes of *in vitro* testing. If the teachings of Lewis were adopted, the skilled artisan would be motivated to prepare a pioglitazone hydrochloride coating that employs a 2:1 ratio of OPADRY® to pioglitazone and apply that coating from a water based suspension. The

above data suggests that such a pioglitazone coating, when applied to a sustained release coated metformin core, may not adhere to the sustained release coating and release not less than 90% of the pioglitazone within 30 minutes of *in vitro* testing.

Based upon the foregoing amendments and representations, Applicants respectfully request that the rejection of the claims under 35 U.S.C.§ 103(a) be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

/martin p. endres/

Martin P. Endres
Reg. No. 35,498

MAILING ADDRESS:
FLOREK & ENDRES PLLC
1156 Avenue of the Americas
New York, NY 10036
(212) 997-1000